Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

Adverse Event Reporting For Dietary Supplements

An Inadequate Safety Valve

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EXECUTIVE SUMMARY

PURPOSE

To assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in protecting the American consumer.

BACKGROUND

Dietary supplements are increasingly popular. Currently about 60 percent of Americans take some form of dietary supplement every day without any apparent problems. Supplements include substances such as vitamins, minerals, botanicals, and amino acids. Although many of these supplements can be beneficial, there are risks associated with some. For example, ginkgo biloba may lead to excessive bleeding, vitamin A in high dosages during pregnancy may lead to birth defects, and St. John's Wort may reduce the effectiveness of some antiviral drugs. Unlike new prescription and over-the-counter drugs, FDA does not have the authority to require supplements to undergo premarket approval for safety and efficacy. Instead, it relies mostly on its adverse event reporting system to identify safety problems.

FDA's Adverse Event Reporting System for Dietary Supplements

FDA's adverse event reporting system for dietary supplements includes (1) detecting adverse events, (2) generating signals of possible public health concerns, (3) assessing those signals, and (4) taking appropriate safety actions based on its assessment. An adverse event is an incident of illness or injury that *may* be associated with a product or ingredient. With further investigation, the association may or may not be confirmed. Reporting adverse events is entirely voluntary, and FDA receives reports from a variety of sources including consumers and health professionals.

When a signal of a possible health problem is generated from the adverse event reporting system, FDA assesses whether it is an actual public health problem warranting attention. FDA can assess these signals by reviewing scientific literature, consulting with experts, reviewing clinical data, conducting its own laboratory tests, and/or commissioning studies. If FDA confirms that a public health problem exists it can take a range of safety actions, such as issuing warnings to consumers and health professionals, issuing import alerts, requesting product recalls, or seizing products.

This Inquiry

In this report, we evaluate how well FDA's adverse event reporting system for dietary supplements functions as a consumer protection tool. We analyzed data from FDA's database; reviewed FDA laws, regulations, policies, and procedures; reviewed several adverse event reports; reviewed relevant literature; and interviewed FDA officials, industry representatives, and scientific experts. We did not evaluate the internal

operating procedures of the system.

FINDINGS

FDA's adverse event reporting system detects relatively few adverse events.

Adverse event reporting systems typically detect only a small proportion of the events that actually occur. This appears to be especially true of FDA's system for dietary supplements. A recent FDA-commissioned study estimated that FDA receives less than 1 percent of all adverse events associated with dietary supplements. Among the factors that may contribute to under-reporting are that many consumers presume supplements to be safe, use these products without the supervision of a health care professional, and may be unaware that FDA regulates them. FDA's limited outreach concerning this system contributes to this unawareness.

It has difficulty generating signals of possible public health concerns.

FDA lacks much of the information that is necessary to effectively analyze adverse event reports and to generate possible signals of concern. Below we document the lack of information by presenting FDA data between 1994-1999.

Limited medical information. FDA did not receive the medical records for 58 percent (464 of 801) of the reports for which it requested them. Only 20 percent (527 of 2,547) of adverse events reports received by FDA came from health professionals.

Limited product information. FDA was unable to determine the ingredients for 32 percent (1,153 of 3,574) of the products mentioned in adverse event reports. FDA does not have the product labels for 77 percent (2,752 of 3,574) of the products mentioned in reports. FDA does not have product samples for 69 percent (130 of 188) of the products for which it requested them. Product samples are especially helpful because dietary supplement ingredients are not standardized.

Limited manufacturer information. FDA reports that it has received fewer than 10 adverse event reports directly from manufacturers. FDA was unable to determine the manufacturer of dietary supplement products for 32 percent (1,153 of 3,574) of the products involved in reports. FDA was unable to determine the city and State for 71 percent (644 of 904) of the manufacturers.

Limited information on the dietary supplement consumer. FDA was unable to follow-up with 27 percent (214 of 801) of the reports it tagged for follow-up primarily because the reports lacked sufficient information to identify the alleged injured party.

Limited ability to analyze trends. FDA has difficulty analyzing trends of adverse event reports because its lacks an adequate computer database for routine analysis and receives relatively few reports.

FDA lacks vital information to adequately assess signals of possible public health concerns generated by the adverse event reporting system.

In order to assess such signals, FDA must draw upon key information external to the system. But FDA faces obstacles in obtaining such information. For a recent case study that documents these obstacles see appendix A.

Limited clinical information. There is some clinical information available on dietary supplements and more is becoming available every day. But, the current regulatory framework for dietary supplements permits manufacturers to market a supplement without premarket safety studies. For this and other reasons, FDA has relatively little clinical information on particular products. The law requires manufacturers of certain new dietary ingredients to notify FDA 75 days prior to market and include "relevant" safety information. However, very few dietary ingredients are subject to this requirement, and FDA has issued no guidance on the type of safety information that should be submitted.

Limited information on consumer use. FDA lacks a mechanism to track the number of consumers using a particular supplement. Such information can be helpful to determine the incidence of certain adverse events in the user population and thus, the extent of the public health problem that it poses.

As a result, FDA rarely takes safety actions related to the adverse event reporting system.

Safety actions can be of significant benefit to consumer safety. For example, based on FDA's investigation of adverse event reports, it found products containing plantain were contaminated with *Digitalis lanata*, a plant that can cause heart attacks in certain individuals. FDA issued a consumer warning against certain products containing plantain and asked supplement manufacturers to voluntarily recall their products contaminated with *Digitalis lanata*.

But, between January 1994 and June 2000, we were able to document only 32 safety actions that FDA took based on the adverse event reporting system—a period when more than 100 million people were taking supplements. With limited information to draw upon to generate and assess signals, FDA rarely reaches the point of knowing whether taking a safety action is warranted.

Public disclosure of adverse event reports can also be considered a type of safety action. FDA uses its website as its main vehicle for disclosure. However, its website has significant limitations; for example, it provides no evaluation of the reports, contains misleading information, and is rarely updated.

RECOMMENDATIONS

Our evaluation of FDA's dietary supplement adverse event reporting system leads us to conclude that without further development of the overall regulatory framework for

dietary supplements, the potential of the system to serve as a consumer safeguard is inherently limited. The program simply cannot serve as an adequate safety valve until other measures are taken that will allow FDA to generate and confirm signals of possible public health concerns.

Below we offer our recommendations as a blueprint for actions that FDA can take over a reasonable period of time. It has already called for some of them in its strategic plan for dietary supplements. We recognize that some of our recommendations will call for legislative or regulatory changes. We also recognize that resources are limited and that some of our recommendations may require additional resources.

RECOMMENDATION 1: Facilitate greater detection of adverse events.

Require dietary supplement manufacturers to report serious adverse events to FDA for some products. FDA should examine what types of products or ingredients should fall under this requirement. FDA already requires pharmaceutical manufacturers to report adverse events for all prescription and some over-the-counter drugs.

Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements. These centers hold information that may be useful to FDA. Reports from Poison Control Centers may provide additional data to help generate signals of possible public health concern.

Inform health professionals and consumers about the adverse event reporting system for dietary supplements. The main way FDA can accomplish this is by expanding its outreach to health professionals and including information about the safety actions it has taken. Other possibilities include requiring manufacturers to provide a toll-free number on their product labels or placing FDA's toll-free number on labels.

RECOMMENDATION 2: Obtain more information on adverse event reports in order to generate stronger signals of public health concerns.

Educate health professionals about the importance of including medical information in adverse event reports. Without medical information about the alleged injured parties, FDA lacks crucial information for determining the likelihood that an adverse event was related to the use of a dietary supplement. When FDA conducts outreach it should encourage health processionals to obtain permission from their patients to release their medical records when appropriate.

Require dietary supplement manufacturers to register their products with FDA. A complete product registry would allow FDA to instantly access a list of all of the ingredients in a particular product and determine the product manufacturer's name as soon as it receives an adverse event report.

Require dietary supplement manufacturers to register with FDA. A registry of manufacturers would enable FDA to quickly and easily contact a manufacturer whose product was associated with an adverse event to obtain additional information.

Notify manufacturers when FDA receives a serious adverse event report. Alerting manufacturers of adverse events in which their products have been mentioned would give FDA the opportunity to obtain more product information from the manufacturer. It would also allow manufacturers to reevaluate the safety profile of the product, including manufacturing procedures, in a timely manner.

Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party. Without this information FDA may be unable to gather additional information excluded from the report.

Develop a new computer database to track and analyze adverse event reports. To help identify signals, FDA needs a database that allows for querying by ingredients as well as products and types of adverse events.

RECOMMENDATION 3: Obtain vital information to adequately assess signals generated by the adverse event reporting system.

Issue guidance on the type of safety information that manufacturers should include in the 75-day premarket notification requirement for some new dietary supplement ingredients. FDA should take full advantage of its existing authority to obtain as much safety information as possible prior to marketing.

Explore the possibility of a monograph system for dietary supplements that would contain safety information on particular ingredients. Monographs are point papers on particular ingredients that contain safety and efficacy information. Such a system would allow FDA to have in a systematic fashion safety information that it could rely upon to help make decisions.

Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues. Another way that FDA can gain clinical information is by collaborating with the National Institutes of Health that funds and conducts research related to dietary supplements.

Assist industry and the United State Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals. Standardized ingredients would allow FDA to have the confidence that in taking action against unsafe products or ingredients it is addressing all the products posing a health risk.

Expedite the development and implementation of good manufacturing practices for dietary supplement manufacturers. Standardized ingredients must be complemented by FDA enforcing those standards through good manufacturing practices. These are essential for FDA to be assured of the precise contents of each batch of supplements that is manufactured.

RECOMMENDATION 4: Disclose more useful information to the public about dietary supplement adverse events.

FDA should provide more useful data on its website so that consumers can, to some extent, evaluate the likelihood that the adverse event was related to the supplement. FDA could update the information on its website more regularly. FDA could also accomplish this is by providing summary data on the numbers and types of reports received by product types or ingredients. Over time, as resources become available it could consider indicating the likelihood the event was caused by a product.

COMMENTS

We received comments on our draft reports from the Food and Drug Administration. We also solicited and received comments from three trade associations (Consumer Healthcare Products Association, American Herbal Products Association, and the Council for Responsible Nutrition) and two public interest organizations (Public Citizen's Health Research Group and the Center for Science in the Public Interest.) See appendix C for the comments in their entirety.

On the basis of these comments we made several changes that are reflected in this final report. Some involved minor technical changes, and others involved brief elaborations to clarify and add context. In two instances we modified our recommendations to target them more effectively and to minimize regulatory burden. We limited the scope of mandatory reporting of adverse event reports to events that are both serious in nature and fall under a certain subset of products to be determined by FDA. Similarly, instead of calling for FDA to notify manufacturers of all adverse event reports it receives, we called for it to notify the manufacturers of serious reports only.

Food and Drug Administration

FDA reported that our findings were a fair assessment of the challenges it faces. It also agreed with the majority of our recommendations. As part of its comments, it categorized our recommendations into three areas: (1) tasks that it can currently accomplish, (2) tasks that require additional resources, and (3) tasks that require both legislative changes and additional resources. FDA documented the progress it has made in each of these categories. FDA indicated that the major difficulty it faces to improving the system is a lack of adequate resources.

FDA is making progress toward improving the system along the lines we call for in our report. Many of our recommendations are already included among FDA's top priorities for the year as well as in its 10-year strategic plan. We also encourage FDA to seek the authority it needs to require manufacturer and product registration and mandatory manufacturer reporting of adverse events.

Trade Associations

The three trade associations provided some support for our recommendations, but for the most part, they were highly critical of both our findings and recommendations. While we disagree with the thrust of their comments, they help sharpen the issues that need to be addressed as part of any reform.

One of their major critiques was that we chose not to evaluate the internal operating procedures of FDA's adverse event reporting system, thereby leaving us with little basis for our broader recommendations. We agree that there could be value to a procedural review. FDA should be doing everything it can to make sure the current system operates as effectively as it possibly can. However, we offer strong evidence that the current system is fundamentally flawed and cannot provide an adequate consumer safeguard unless FDA is given more tools to do the job.

Another significant critique was that we failed to view dietary supplements in the context of a food-related system. This failure, they claim, led us to call for more extensive oversight, similar to that for prescription drugs. Our inquiry focused on how the current system was functioning and made us acutely aware of just how little information FDA has available to determine whether adverse events about dietary supplements (however characterized) present danger signs that should be addressed. Without an improved capacity to obtain such information, FDA's adverse event reporting system will continue to fall short of its potential.

Still another critique was that our report reflects a negative view of dietary supplements and fails to recognize their role as self-care products that so many consumers value. We regret any implication of such a negative view. If the kind of recommendations we call for are enacted, we suggest that consumers would have more extensive and useful information available to them on these self-care products and could have more confidence that an adverse event reporting system was providing them with a valuable measure of protection.

Public Interest Organizations

The two public interest organizations strongly supported our report. Their main critique was that we did not go far enough. One called for legislative changes that, over time, would significantly enhance FDA authorities. The other called for FDA to support a systematic study of dietary supplement safety and efficacy. While our evidence did not allow us to go as far as these organizations would like, it did lead us to emphasize that a comprehensive set of changes must be carried out if the adverse event reporting system is to provide an adequate consumer safety valve.